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# Acoustic Droplet Ejection Enabled Automated Reaction Scouting

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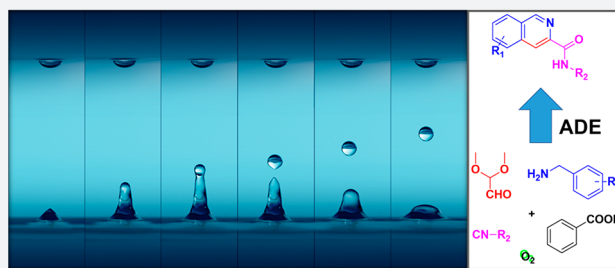
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## S Supporting Information

**ABSTRACT:** Miniaturization and acceleration of synthetic chemistry are critically important for rapid property optimization in pharmaceutical, agrochemical, and materials research and development. However, in most laboratories organic synthesis is still performed on a slow, sequential, and material-consuming scale and not validated for multiple substrate combinations. Herein, we introduce fast and touchless acoustic droplet ejection (ADE) technology into small-molecule chemistry to transfer building blocks by nL droplets and to scout a newly designed isoquinoline synthesis. With each compound in a discrete well, 384 random derivatives were synthesized in an automated fashion, and their quality was monitored by SFC-MS and TLC-UV-MS analysis. We exemplify a pipeline of fast and efficient nmol scouting to mmol- and mol-scale synthesis for the discovery of a useful novel reaction with great scope.



New materials and drugs are discovered by sequential optimization of properties involving the synthesis and testing of many different chemicals. There is an urgent need for acceleration and miniaturization of synthetic organic chemistry in the quest for new synthetic methodologies.<sup>1–4</sup> New library design in the pharmaceutical industry intends to overcome the monotonous use of a few validated robust organic reactions.<sup>5–7</sup> The overuse of the 20 most popular reactions in medicinal chemistry leads to a limited, crowded, and narrow chemistry space.<sup>8</sup> However, new synthetic methodologies result in making and exploring structures that were previously inaccessible.<sup>9,10</sup> Commercial availability of reagents, high robustness of the reactions, and a pressure on delivery were proposed as reasons for the overuse of some handful of reactions, while many new synthetic methodologies are neglected.<sup>11</sup> Often reaction discovery and optimization are done in a sequential fashion, and scope and limitations are not elaborated; however, rather simple derivatives with high yields are presented in the initial report of novel synthetic methodologies. “Real-world” syntheses involving more complex building blocks then often disappointingly show severe limitations in substrate scope. Therefore, miniaturization, automation, and resulting acceleration of synthetic chemistry is an emerging field.<sup>12–17</sup> Recent applications of high-throughput experimentation (HTE) in synthetic chemistry included the scope and limitation and catalyst optimization of well-known two-component C–C, C–N, and C–O cou-

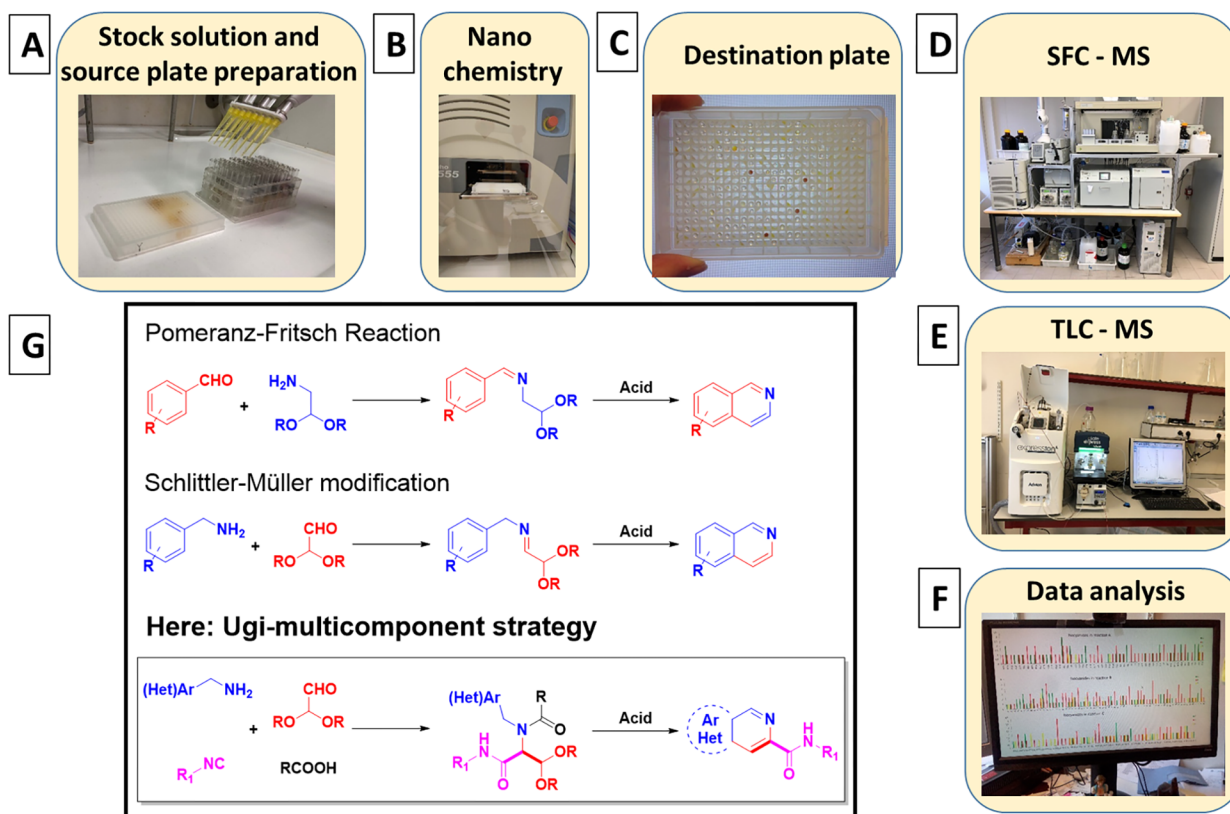
plings.<sup>18,19</sup> Established methods of miniaturized synthesis include flow-chemistry<sup>20–23</sup> and positive displacement liquid handling.<sup>24,25</sup> Here, we introduce for the first time acoustic droplet injection (ADE) for the fast and touchless nL-volume transfer of reagents to probe a new isoquinoline synthesis for the synthesis of a large number of discrete and novel compounds in a short time. In ADE, short and precise acoustic waves are applied to a liquid, and very small nanodroplets of defined size are ejected and transported to a destination.<sup>26</sup> Specific advantages of ADE over other microfluidic or positive displacement liquid handling technologies include very low droplet volumes of 2.5 nL, very high accuracy, unprecedented fast reagent transfer (~200 Hz) leading to the fast reagent pipetting for combinatorial as well as random libraries, and eliminating any sources of cross-contamination.<sup>27</sup>

Our design is based on the combination of the Ugi four-component reaction,<sup>28</sup> the Pomeranz–Fritsch reaction,<sup>29,30</sup> and the Schlittler–Müller modification<sup>31,32</sup> to potentially pave an attractive novel pathway to synthesize diverse isoquinolines. We envisioned broadly accessing substituted isoquinolines and heterocyclic derivatives by the use of the bifunctional monoprotected 2,2-dimethoxy acetaldehyde as a key component in the Ugi reaction followed by an acid hydrolysis and

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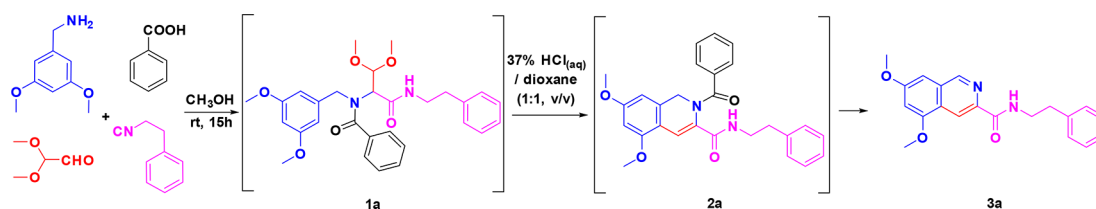
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**Figure 1.** Experimental workflow of nanochemistry and design of reaction. (A) Stock solution and source plate preparation with the required building blocks. (B) Nanodroplet acoustic droplet ejection transfer with Echo 555 system. (C) Destination 384-well plate after compound transfer. Analytics of the synthesis plate by (D) SFC-MS, and (E) TLC-MS. (F) Data analysis. (G) Classical isoquinoline syntheses and the newly designed isoquinoline synthesis.

### Scheme 1. Optimized Condition for Ugi/Schlittler–Müller Reaction

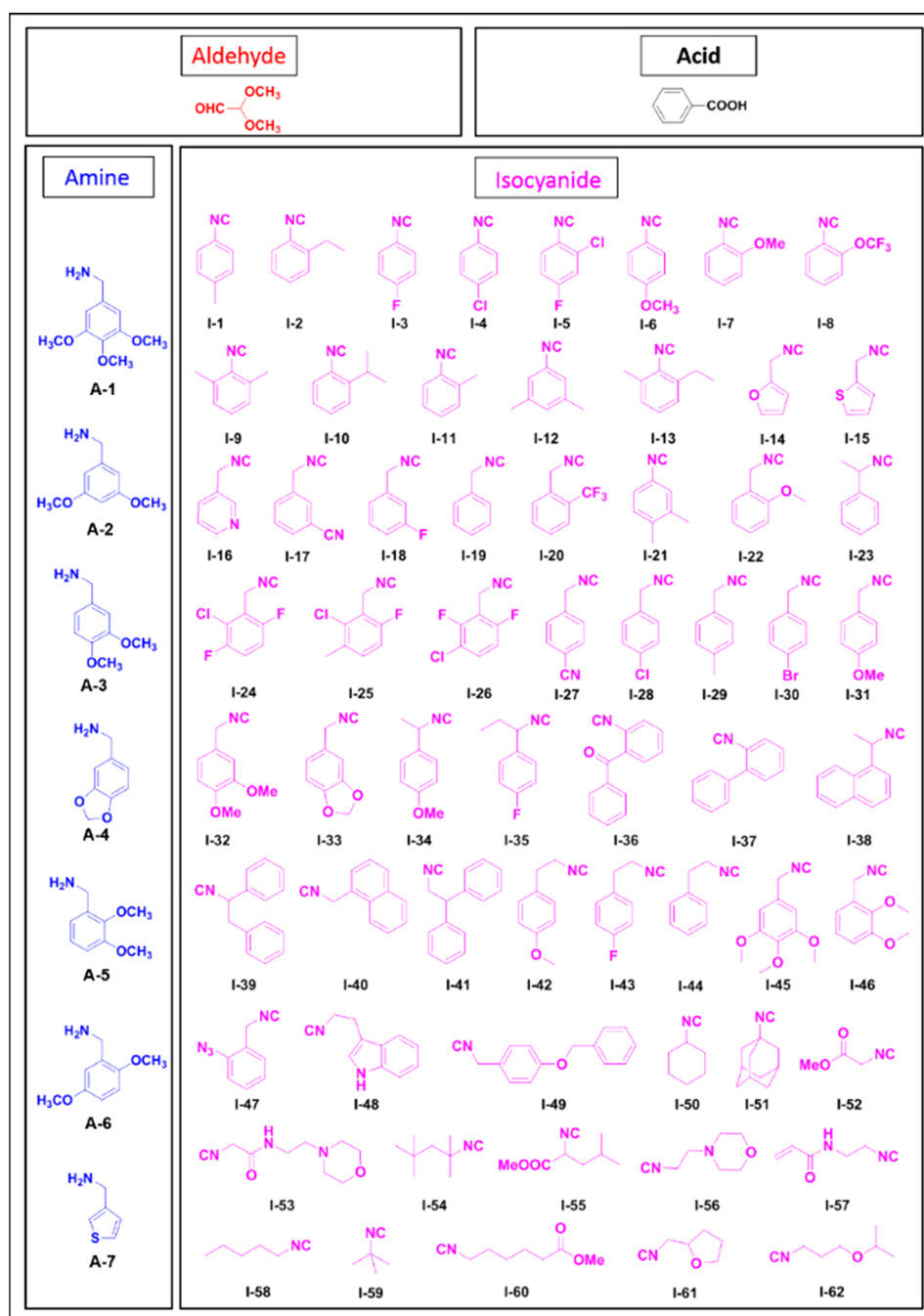


spontaneous oxidation step (Figure 1G). Unlike the classical multistep sequential isoquinoline syntheses, variation on the phenyl and the amide part could be performed at the same time in a one-pot fashion. Thus, a much greater chemical space could be possibly accessed more efficiently when performed on the automated and miniaturized ADE technology platform (Figure 1A–F).

Thus, we first performed and optimized the proposed reaction and the subsequent acid-catalyzed cyclization/oxidation reaction on a mg scale using 3,5-dimethoxybenzylamine, 2,2-dimethoxyacetaldehyde, benzoic acid, and phenylethyl isocyanide. The best conditions for the cyclization were methanol as the solvent for the Ugi reaction and 37%  $\text{HCl}_{(\text{aq})}$  solution in dioxane (1:1, v/v) affording the isoquinoline 3a in 68% yield (Scheme 1, Table S1). It is noteworthy that the reaction runs under very mild conditions at room temperature.

To thoroughly investigate the substrate scope and limitations in a rapid way, we envisioned using the nL-volume ADE technology to build a random library of isoquinolines.<sup>33</sup> Thus, we used 7 different benzyl amines including heterocyclic

derivatives and 62 isocyanides as building blocks (Figure 2, Figure S2). The theoretically possible combinations of substrates can result in 434 different isoquinolines. To accelerate and facilitate synthesis and analytics, the preparation of a random library of isoquinolines in a 384-well plate was performed. The reactants were dissolved as 0.5 M ethylene glycol stock solutions in a polypropylene (PP) source plate and were dispensed via ADE into a PP 384-well destination plate using an Echo 555 acoustic dispenser to yield 3000 nL final volume per well. Then, 375 nmol of each starting material (750 nL of 0.5 M stock solution) was transferred to the destination plate which theoretically results in 375 nmol of product in the case of 100% yield (page S5, Supporting Information). Ethylene glycol was the solvent of choice with a low volatility and otherwise similar properties to methanol, which is the typical solvent for Ugi reactions. The total transfer time was ~150 min. The sealed plate was shaken for 12 h when 10  $\mu\text{L}$  of 37%  $\text{HCl}_{(\text{aq})}$ /dioxane solution (1:1, v/v) was added. The plate was kept at room temperature for another 12 h. Then, the plate was dried of the solvent by applying a mild stream of nitrogen.

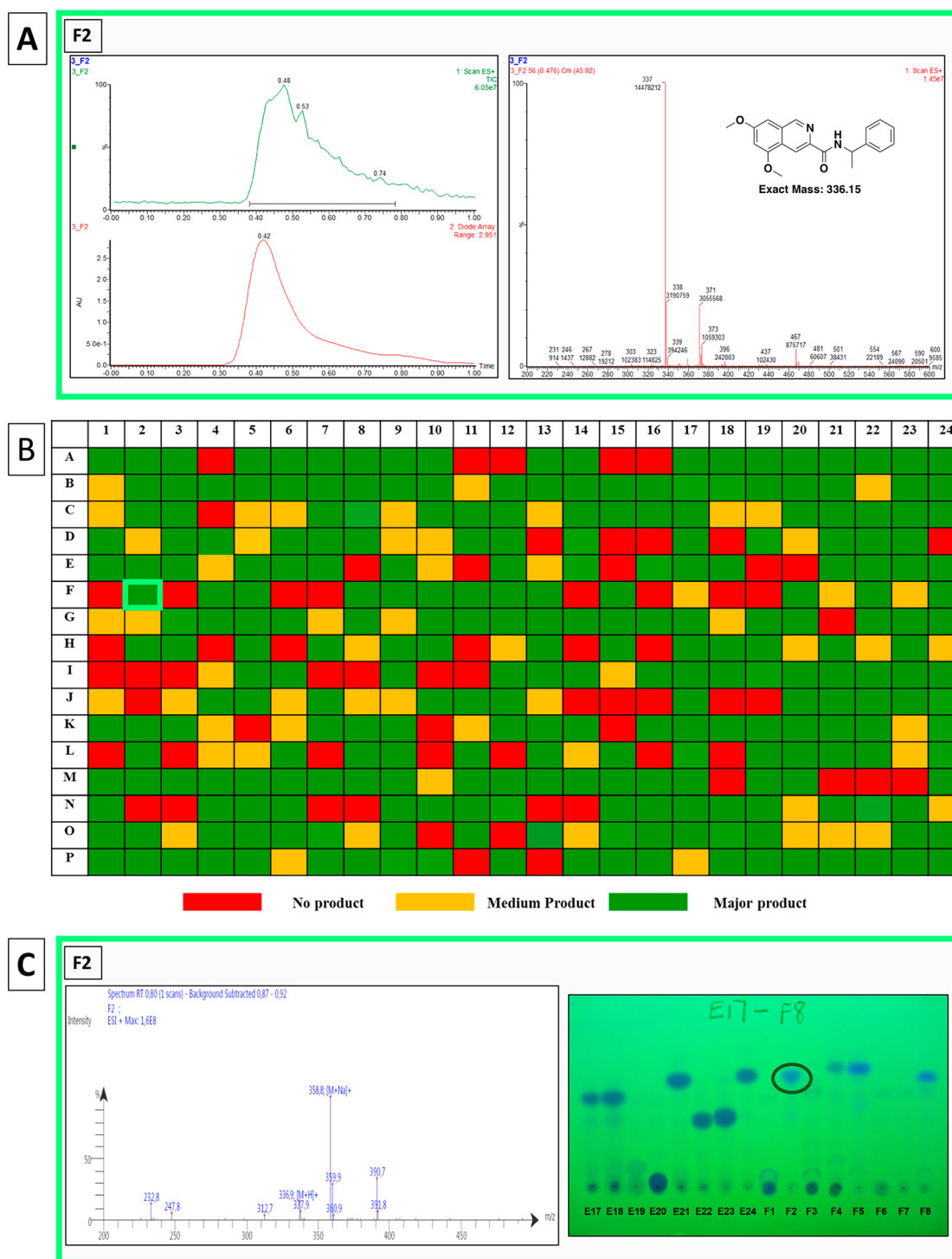


**Figure 2.** Building blocks used for the new isoquinoline synthesis.

The analytics of all wells was performed by two complementary methods, supercritical fluid chromatography (SFC-UV-MS) and thin-layer chromatography (TLC-UV-MS) (Figure 3; page S13, Supporting Information). The SFC analytic of one well takes  $\sim 1$  min, resulting in an overall measuring time for the 384-well plate of less than one night (page S13, Supporting Information).

A qualitative indication of the reaction performance was obtained by analyzing the MS of the product in the SFC (Figure 3A,B). Moreover, we were investigating all wells by TLC-UV-MS as a complementary method (Figure 3C). The TLC-UV-MS of all 384 wells was performed in less than 5 h. Good agreement was found between the two different analytical methods. We found that the majority of the

reactions worked very well, and the main peak in the chromatograms corresponded to the expected products. More than 80% of the reactions gave the corresponding products (Scheme S4). All electron-rich benzylamines (A1–6) and the heterocyclic thiophene derivative A7 reacted similarly well. The compatibility of the isocyanides was surprising. A great diversity of not commonly used isocyanides reacted well, including primary linear, bulky tertiary aliphatic, aromatic, substituted benzylic, heterocyclic, and amino-acid-derived isocyanides. Functional group compatibility involved halogens, nitrile, ether, ketone, allyl, amide, ester, and acrylamide, including several multifunctional derivatives. A total of 68 reactions failed (18%, red designation).

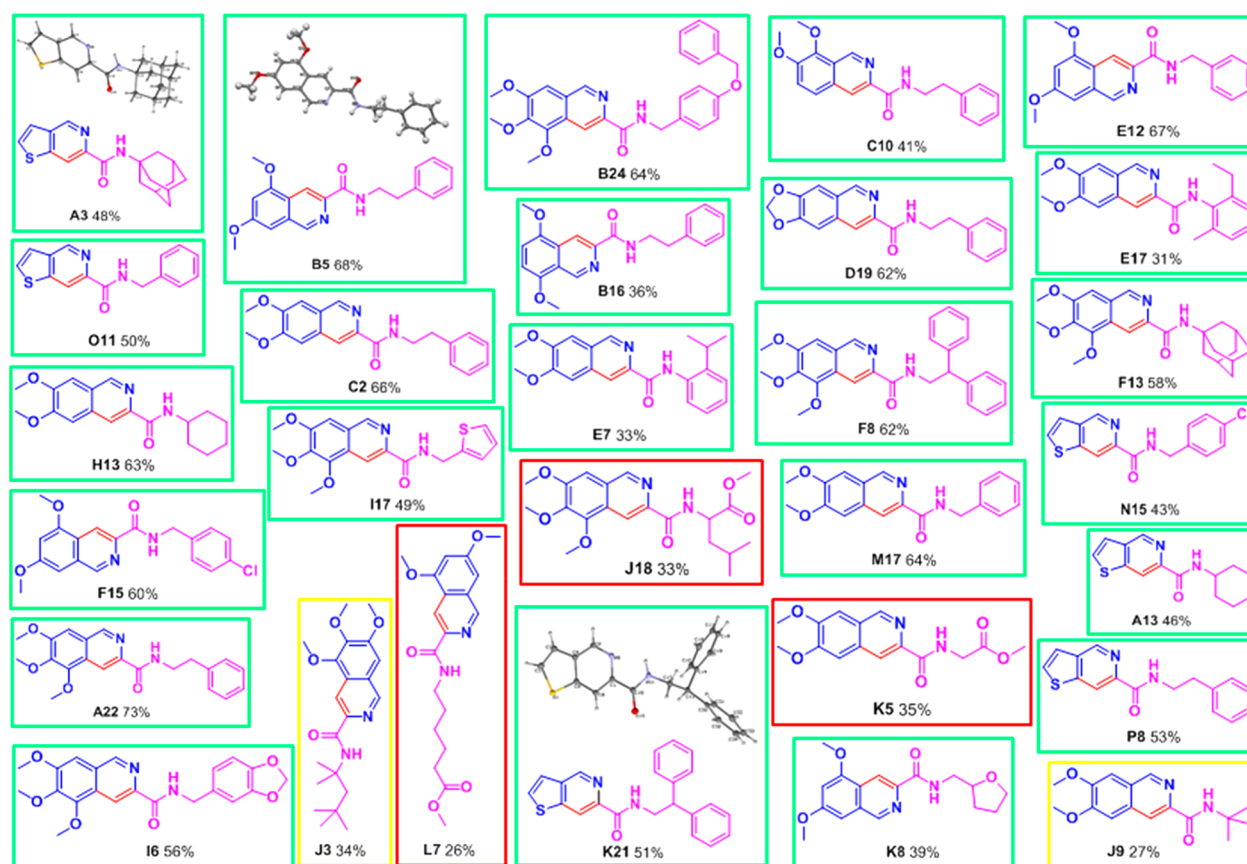


**Figure 3.** Chemical space accessed by ADE-enabled isoquinoline scouting. Exemplary analysis of well F2 by (A) SFC and (C) TLC-UV-MS. (B) Heat map of a 384-well plate based on SFC-UV-MS analysis. In the mass chromatogram, if the peak corresponding to M+1 was the major peak, the well was given a green designation, and otherwise yellow. If the peak of M+1 was absent, the well was given a red designation.

Out of 62 investigated isocyanides only 7 did not react at all (11%, **I47**, **I48**, **I52**, **I53**, **I55**, **I56**, **I60**). We found that the two morpholinoethyl-containing isocyanides (**I53**, **I56**) reacted well in the Ugi reaction; however, no reaction was detected in the following cyclization/oxidation step, even by repeating the reaction on a mg scale. *o*-Azido benzylisocyanide (**I47**) also did not react in all seven cases. Azido groups are known to be unstable under highly acidic conditions and might decompose under the cyclization conditions. Moreover, indole-containing

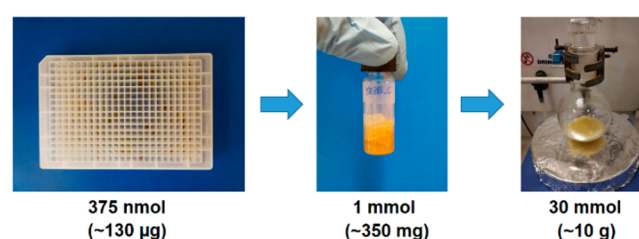
isocyanide (**I48**) did not show the expected mass of the product. We speculate that the indole moiety under the highly acidic conditions is undergoing secondary reactions such as Pictet–Spengler-type reactions. All methyl ester substituted isocyanides (**I52**, **I55**, **I60**) are designated red in the heat map despite showing the product, however, as transesterification toward the glycol esters. Clearly, the ADE-enabled HTE gives valuable insight into building block combination which otherwise are not amenable in a reasonable time frame.





**Figure 4.** Structures and representative X-ray structures of the isoquinolines resynthesized on a mmol scale selected from the plate according to the analytical performance.

Scalability of a reaction over several orders of scale is not automatically given. Therefore, to demonstrate the scalability of nmol-based results of the ADE technology, we scaled randomly chosen reactions of the 384-well plate to multi-mg scale (Figure 4, Figure S3). We resynthesized a library of 29 isoquinolines and heterocyclic derivatives in 26–73% isolated yields by probing various electron-rich benzylamines, thiophene methylamine, and isocyanides. Among the resynthesized compounds, 17 different isocyanides and 6 different benzyl amines as starting material were reacted. For example, 3-(isocyanomethyl)-tetrahydrofuran which led to interesting product **J3** with hydrophilic tetrahydrofuran side chain worked well. The methylester containing products (**J18**, **K5**, and **L7**) gave clean products in 35%, 33%, and 26% yields, respectively. The introduction of the amino acid ester isocyanides can be beneficial for further modifications to synthesize diversified scaffolds and more complex peptide mimetics. Moreover, the thienopyridine scaffolds (**A3**, **A13**, **K21**, **N15**, **O11**, **P8**), which are known for their anticancer and antiplatelet activities,<sup>34,35</sup> were constructed with moderate to good yields (43–53%) in just one step. The structures of several novel isoquinoline products and thus novel reactions were confirmed by X-ray crystallography (Figure S5). To further underscore the scalability of the new isoquinoline synthesis, we performed a multigram 30 mmol synthesis of **C2** (Figure 5, Figure S4). Gratifyingly, the reaction product precipitated out (72% yield) after overnight stirring of the Ugi-adduct under acidic conditions. In addition, the obtained product was 89% pure without any column chromatography, determined by quanti-



**Figure 5.** Scalability: from  $\mu\text{g}$ -scale scouting to mg- and g-scale synthesis.

tative NMR (qNMR) using benzyl benzoate as internal standard (pages S133 and S135, Supporting Information).

Thorough investigation of scope and limitation of a novel reaction are a major challenge in contemporary synthetic chemistry because many different combinations of differentially substituted building blocks have to be reacted.<sup>6</sup> It is, however, of uttermost importance to be adopted by end-users. Functional group tolerance of the reactions limits the scope of structure–activity studies. Seemingly small local steric, electronic, or stereoelectronic effects imposed by diverse functional groups in the starting materials often have dramatic effects on the outcome of the reaction.<sup>8,9,19</sup> It is believed that the major hurdle to the application of a new chemical methodology to real synthetic problems is a lack of information regarding its application beyond the idealized conditions of the seminal report. Therefore, robustness screens, e.g., for the rapid assessment of catalytic reactions have been proposed which used different equimolar additives

in the presence of a simple reaction to monitor their interference.<sup>36</sup> We herein pursued a different path of reaction scouting by randomly performing different reactions based on a real-world selection of multiple building blocks with many different functional groups potentially interfering with the reaction at a miniaturized nmol scale. To exemplify this technology, we have used automated ADE to scout a newly designed isoquinoline synthesis. The miniaturized high-throughput technique allows for the rapid synthesis of libraries of compounds on a nmol scale. In less than 2 days, 384 reactions were performed including quality evaluation of each reaction by SFC-MS and TLC-UV-MS. An unprecedented large number of 62 substituted isocyanides were randomly combined with 7 different benzylamines to evaluate the chemical reaction space. The great majority (~80%) of the nanoscale reactions revealed the product. Probing highly substituted starting materials revealed a great functional group compatibility including hydrophilic moieties. This is of high importance to gain access to druglike properties, e.g., metabolic stability and solubility in body liquids. Resynthesis of 29 examples on a traditional mmol scale was performed in good to excellent yields, showing the scalability of the reaction. Another example was synthesized on a ~10 g scale. This approach is in contrast to the classical reaction evaluation where only a small number of derivatives are synthesized on a mmol scale, in low-density reaction arrays, and little information about the scope of a reaction is generated. Advantages of the synthesis technology include not only fast and fair assessment of the scope of a new reaction but also overall very low material consumption. This allows the inclusion of precious starting materials, e.g., the majority of the isocyanides used. The total amount of building block material used in the successful synthesis of >300 unprecedented isoquinolines is less than 50 mg.

Million-sized screening libraries of pharmaceutical companies are still built on mg amounts of purified compounds. Therefore, periodical renewal of the library content is a synthetic and logistic challenge. An application of the herein described automated nanoscale ADE-enabled synthesis can be envisioned to be a rapid and efficient prescreen of the chemical space of a novel reaction. With this, synthesizable compounds may be rapidly identified at a nanomole-scale to select compounds for mg scale-up including time-consuming reaction purification to fill the screening decks of pharmaceutical and agrochemical companies for the discovery of novel bioactive compounds. Recent computer-assisted synthetic advancements including artificial-intelligence-driven synthesis planning and structure-based machine learning reactivity prediction describe a pathway to automated and accelerated synthesis.<sup>37</sup> However, it remains a significant challenge to devise automated wet-lab synthesis without extensive and lengthy optimization.<sup>16</sup> Synthetic organic chemistry with an almost infinite number of reactions and associated reaction conditions for now remains a largely experimental science, which our technology platform is well-positioned to accelerate.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.8b00782.

Nanomole-scale synthesis instrumentation, procedures, quality control, statistical analysis, mg- and g-scale synthesis general procedure, <sup>1</sup>H and <sup>13</sup>C NMR spectra, HRMS, and crystallographic data (PDF)

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### Author Contributions

<sup>†</sup>Y.W. and S.S. contributed equally to this work.

### Notes

Safety statement: no unexpected or unusually high safety hazards were encountered in this line of research.

The authors declare no competing financial interest.

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